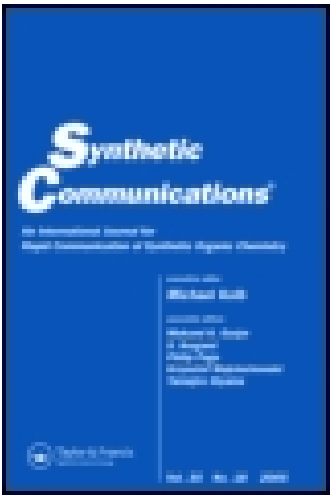

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Chlorination of 2-Chloroquinoline-3-carbaldehydes

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CHLORINATION OF 2-CHLOROQUINOLINE-3-CARBALDEHYDES

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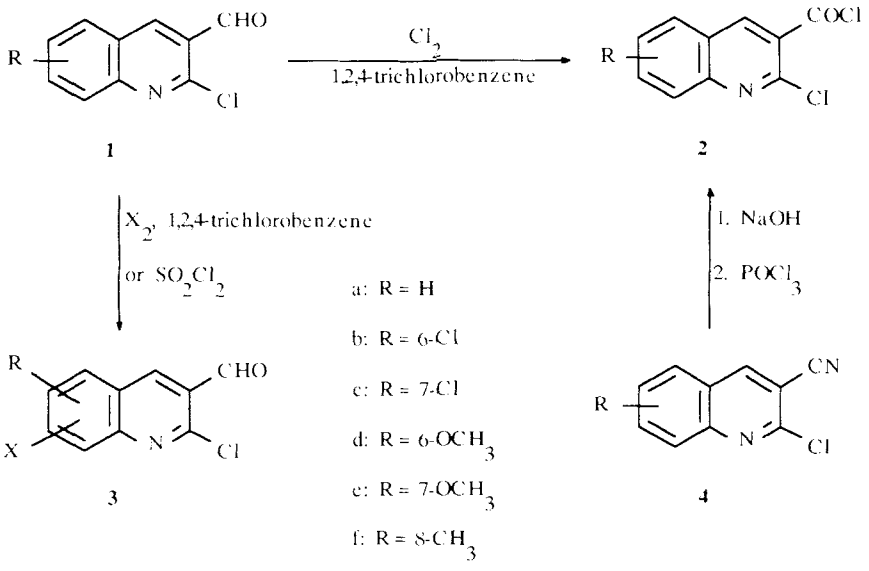
Abstract: *Reactions of 2-chloroquinoline-3-carbaldehydes (1) with chlorine, thionyl chloride and sulphuryl chloride are investigated. Preparation of 2-chloroquinoline-3-carbonyl chlorides (2) and 2-chloro-3-dichloromethylquinolines (5) as products of these reactions is described.*

Reactions of 2-chloroquinoline-3-carbaldehydes (1) have been thoroughly investigated during the last few years[1,2,3] and a number of 2-chloroquinoline-3-carbaldehyde derivatives have been prepared possessing biological activity[4].

We wish now to report on the results of the chlorination of 2-chloroquinoline-3-carbaldehydes (1) with chlorine, thionyl chloride and sulphuryl chloride. It is known that 2-chlorobenzoyl chloride can be prepared by treatment of 2-chlorobenzaldehyde with chlorine without solvent[5] at 140-160°. We have found that 2-chloroquinoline-3-carbaldehydes (1) having no or chlorine substituents in the homoaromatic ring can be chlorinated with chlorine gas directly to 2-chloroquinoline-3-carbonyl chlorides (2) in good yields. The reactions were performed in 1,2,4-trichlorobenzene at 120-130° for 2 hours (Scheme 1, Table 1). Similar treatment of 7-bromo-2-chloroquinoline-3-carbaldehyde afforded two products, namely 7-bromo-2-chloroquinoline-3-carbonyl chloride and 2,7-dichloroquino-



Scheme 1

line-3-carbonyl chloride (2c) in 1:1 ratio because of the change of the bromine by chlorine.

This method was unsuccessful in the case of methyl- or methoxy-substituted quinolines 1. Compounds 1 having methyl group in the homoaromatic ring gave a complex mixtures on treatment with chlorine. The corresponding acid chlorides can be prepared in an indirect way (Scheme 1). For example, hydrolysis of 2-chloro-3-cyano-8-methylquinoline (4f) followed by treatment with $POCl_3$ afforded the corresponding acid chloride 2f in 45 % yield (Table 1).

The action of chlorine on 1d and 1e gave 2,5-dichloro-6-methoxyquinoline-3-carbaldehyde (3d) and 2,8-dichloro-7-methoxyquinoline-3-carbaldehyde (3e), respectively and no formation of acid chloride was observed. The reaction time was 30 minutes under the above mentioned conditions and the starting materials

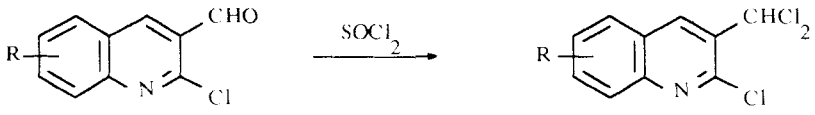
Table 1. Data of compounds prepared.

No.	X	Yield[a]	M.p. (°C)	MS
2a	-	55	98-100[b]	225(M^+,6); 190(100); 162(55)
2b	-	73	164-166[b]	259(M^+,15); 224(100); 196(41)
2c	-	76	135-136[b]	259(M^+,9); 224(100); 196(36)
2f	-	45	113-115[b]	239(M^+,16); 204(92); 63(100)
3d	5-Cl	71	191-193[c]	255(M^+,100); 240(18); 212(44)
3d	5-Br	76	202-204[d]	301(M^+,100); 258(38); 230(24)
3e	8-Cl	81	236-238[c]	255(M^+,100); 219(18); 184(40)
3e	8-Br	78	231-233[d]	301(M^+,100); 221(45); 192(26)
5a	-	77	94-96[e]	245(M^+,11); 210(100); 174(23)
5c	-	71	96-98[e]	281(M^++2,14); 244(100); 208(17)
5e	-	80	92-93[e]	275(M^+,8); 240(100); 197(14)

a:Isolated yield; **b**:THF; **c**:DMSO-ethanol; **d**:ethanol; **e**:chloroform-hexane

underwent chlorination at a position determined by the directing influence of the methoxy group. 3d (X=5-Br) and 3e (X=8-Br) could also be prepared by brominating of 1d and 1e under similar conditions (Table 1) but no reaction occurred when 1d and 1e were treated with iodine.

It is known that sulphuryl chloride is frequently used as a chlorinating agent[6]. It reacts similar to that of chlorine and sometimes to that of phosphorus pentachloride. Reaction of sulphuryl chloride with benzaldehyde affords benzoyl chloride[6]. We have found that 1d and 1e gave 3d (X=5-Cl) and 3e (X=8-Cl)



1 5

Scheme 2

respectively by treatment with sulphuryl chloride at 0°, but no reaction occurred in the case of 1a and 1c even at reflux temperature.

Heating of 2-chloroquinoline-3-carbaldehydes (1) with thionyl chloride gave 2-chloro-3-dichloromethylquinolines (5) in good yields (Scheme 2, Table 2). The reactions were carried out at reflux temperature for 4 hours and there was no need to use DMF or triphenyl phosphine as catalyst in contrast to the known procedures[7,8].

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a Varian Gemini-200 instrument at 200 MHz using TMS as internal standard and chemical shifts are expressed in ppm. Mass spectra were scanned on a VG Trio-2 instrument in EI mode at 70 eV.

2-Chloroquinoline-3-carbonyl chloride (2a) Typical procedure

2-chloroquinoline-3-carbaldehyde (1a) (19.2 g, 0.1 mol) was heated to 120° in 200 ml of 1,2,4-trichlorobenzene. Chlorine was bubbled through the solution with stirring at 120-130° for 2 hrs. After cooling, the solution was evaporated in vacuum (2 Hgmm) and the residue was crystallized from THF.

Table 2. ^{1}H-NMR data of compounds prepared.

No.	X	δ(ppm)
2a[a]	-	7.71(m,1H); 7.95(m,1H); 8.00(m,1H); 8.08(m,1H); 9.00(s,1H)
2b[a]	-	7.85(dd,1H); 7.98(d,1H); 8.02(d,1H); 8.88(s,1H)
2c[a]	-	7.65(dd,1H); 7.94(d,1H); 8.04(d,1H); 8.97(s,1H)
2f[a]	-	2.77(s,3H); 7.57(m,1H); 7.77(m,2H); 8.94(s,1H)
3d[b]	5-Cl	4.06(s,3H); 7.97(d,1H); 8.05(d,1H); 8.82(s,1H); 10.37(s,1H)
3d[b]	5-Br	4.08(s,3H); 7.62(d,1H); 8.05(d,1H); 9.07(s,1H); 10.58(s,1H)
3e[b]	8-Cl	4.12(s,3H); 7.80(d,1H); 8.30(d,1H); 8.96(s,1H); 10.36(s,1H)
3e[b]	8-Br	4.11(s,3H); 7.71(d,1H); 8.33(d,1H); 8.93(s,1H); 10.36(s,1H)
5a[a]	-	7.20(s,1H); 7.60(m,1H); 7.79(m,1H); 7.90(m,1H); 8.01(m,1H) 8.72(s,1H)
5c[a]	-	7.20(s,1H); 7.58(dd,1H); 7.86(d,1H); 8.02(d,1H); 8.71(s,1H)
5e[a]	-	3.94(s,3H); 7.20(s,1H); 7.26(dd,1H); 7.33(d,1H); 7.79(d,1H); 8.63(s,1H)

a: $CDCl_3$; b: DMSO-d_6

2,5-dichloro-6-methoxyquinoline-3-carbaldehyde (3d, X = 5-Cl) Typical procedure

2-chloro-6-methoxyquinoline-3-carbaldehyde (1d) (2.22 g, 0.01 mol) was stirred in 30 ml of 1,2,4-trichlorobenzene at 120-130° for 30 minutes and during this time chlorine was bubbled through the solution. After cooling to 20°, the crystalline product was collected and crystallized from DMSO-ethanol.

2-Chloro-3-dichloromethylquinoline (5a) Typical procedure

2-Chloroquinoline-3-carbaldehyde (1a) (1.92 g, 0.01 mol) was refluxed in thionyl chloride (20 ml) for 4 hrs. The solution was evaporated under reduced pressure and the crude product was crystallized from chloroform-hexane.

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